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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Central Region

Food and Drug Administration
Waterview Corporate Center
10 Waterview Blvd., 3rd Floor
Parsippany, NJ 07054

Telephone (973) 526-6005

September 29, 2003

WARNING LETTER

**CERTIFIED MAIL-
RETURN RECEIPT REQUESTED**

Mr. Michael V. Novinski
President
Organon USA Inc.
56 Livingston Avenue
Roseland, NJ 07068

FILE # 03-NWJ-08

Dear Mr. Novinski:

During an April 24 through June 27, 2003 inspection of your drug manufacturing facility located at 375 Mt. Pleasant Avenue, West Orange, New Jersey, investigators from this office documented serious deviations from current Good Manufacturing Practice (cGMP) Regulations as delineated in Title 21, Code of Federal Regulations, Parts 210 and 211. Deviations were also noted regarding the Postmarketing Adverse Drug Experience (PADE) reporting requirements of Title 21, Code of Federal Regulations, Section 314.80.

The inspection revealed that the Quality and Production systems your firm employs during the manufacture, processing, packing, or holding of Zemuron Injection (rocuronium bromide), do not conform with cGMP. Therefore, the product is adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug and Cosmetic Act (the Act). The following are examples of the significant deficiencies regarding your firm's Quality and Production systems:

1. Failure of the Quality Control Unit to reject drug products which may have been contaminated with metal. [21 CFR 211.22]

Your firm's quality control unit failed to prevent the release of ten lots of Zemuron Injection that were adulterated with metal fragments from your manufacturing equipment. Metal fragments were randomly introduced into thirteen lots of Zemuron Injection after your plant engineers installed the wrong sized filling pump parts on the Zemuron manufacturing line. According to your July 18, 2003 correspondence to this office, the incorrect pump replacement parts allowed metal filling pistons to "...bottom out..." onto metal support blocks. This caused pieces of metal to be scraped into the product. Thirteen lots were produced with the wrong sized parts. The quality control unit rejected

two lots, #3202450 and #3902450, for high particulate matter. Lot #2802450 and part of lot #3302450 were also rejected for sterility test failures. The other ten lots were released to the marketplace, including: #2902450, 3002450, 3102450, 3302450A, 3402450, 3502450, 3602450, 3702450, 3802450 and 4002450.

A thorough analysis of the particulate matter leading to the rejection of lots #2802450 and #3902450 was not conducted, and the quality control unit failed to ascertain a complete characterization of the particles, including maximum size, found in these lots.

2. Failure to assure that equipment used during manufacture will not alter the safety, identity, strength, quality or purity of your drug product. [21 CFR 211.65]

In your firm's response to the FDA-483, dated July 18, 2003, you acknowledge the wrong sized parts were installed in the filling line pump and as a result, metal filling pistons rubbed against metal support blocks during production and pieces of metal were randomly scraped into the Zemuron product.

Prior to changing the filling line pump parts on the Zemuron line, the quality control unit failed to properly assess the impact that the change may have on the product. It is the quality control unit's responsibility to review any change to your manufacturing process and to assure the change will not adversely affect the drug product.

3. Failure to investigate unexplained discrepancies prior to releasing a batch [21 CFR 211.192]

The firm's quality control unit failed to perform an adequate investigation into the metal contamination observed in lot #2802450 and # 3902450. Lot # 2802450 was the first lot manufactured with the wrong sized filling parts, and resulted in a [redacted] vial rejection rate for particulate matter. The quality control unit failed to properly investigate the discrepancy in the rejection rate prior to releasing ten subsequently-produced Zemuron lots. A thorough analysis of the particulate matter leading to the rejection of lots #2802450 and #3902450 was not conducted, and your quality control unit failed to ascertain a complete characterization of the particles, including maximum size, found in these lots.

The quality control unit also failed to adequately investigate the possible correlation between sterility failures found in two of the thirteen lots produced with the incorrect filling parts. According to your annual product review, [redacted] lots of Zemuron injection were manufactured from January 1, 2001 through September 30, 2002. There were three sterility failures resulting in lot rejections during this time period. Two of these lots (#2802450 and #3302450B) were manufactured with the incorrect filling parts. The quality control unit also failed to investigate issues such as container closure integrity or low fill volumes observed by production personnel during the manufacture of lot #2802450.

4. Failure to have written procedures and release specifications for retesting [21 CFR 211.160]

The quality control unit deviated from established release procedures by ordering an added visual test to justify the release of ten Zemuron lots suspected of being contaminated with metal particles. Specifically, after the quality control unit learned that incorrect sized pump parts were installed on the Zemuron line, and knowing that thirteen lots had been produced using the wrong parts, it ordered these lots to be retested. Specifically, it ordered the retesting of [redacted] vials from each lot by [redacted] visual inspection. According to your correspondence to this office, "...this process was used in order to distinguish between batches that were affected by the pump problem and those that were not." The quality control unit had no written protocol or written specifications for this added test, and this retest procedure is not listed as a release specification.

We acknowledge receipt of your July 18, 2003 letter to Ray Abrahams, Director, New Jersey Compliance Branch, containing responses to the June 27, 2003 FDA 483, Inspectional Observations that was issued to your firm. We also acknowledge the September 23, 2003 follow-up letter from Roger C. Schmitt to Compliance Officer Joseph McGinnis. Specifically, we acknowledge your intentions, as stated in your July 18, 2003 correspondence, to voluntarily recall the ten lots of Zemuron Injection that are on the market which were made with the incorrect sized filling parts. In addition, we note your commitment to create written protocols for any special or supplemental testing, the organizational changes you have made in your firm's Quality and Production departments, and your intentions to have each of your individual manufacturing processes certified by a third party consultant as part of your corrective action plan.

However, at the core of the violations is the lack of proper review by the quality control unit to make sure that adequate controls are implemented during manufacturing. For example, you state in your July 18 response that with respect to the distribution of Zemuron vials suspected to be contaminated with metal particles, relevant information was not documented and approved by management before the release determination was made. We consider this function of the quality control unit essential not only in obtaining compliance but also in maintaining the degree of control in your manufacturing processes that is required to assure that the drug manufactured meets the requirements of the Act as to safety, and has the identity and strength and meets the quality and purity characteristics that it purports or is represented to possess.

This inspection also revealed problems with your firm's compliance with the Postmarketing Adverse Drug Experience (PADE) reporting requirements of Section 505(k) of the Federal Food, Drug, and Cosmetic Act ("the Act"), and 21 CFR 314.80.

Based on our review of the inspection report, we conclude that your firm violated Section 301 (e) of the Act because it failed to comply with 21 CFR 314.80 and Section 505 (k)(1) of the Act.

Deviations from the PADE regulations include the following:

1. **Failure to submit to FDA serious and unexpected adverse drug experience reports within 15 calendar days of initial receipt of information. [21 CFR 314.80 (c)(1)(i)]**

Specifically, 107 of 856 cases assessed as 15-day alert reports, received by your firm between 3/11/02 to 5/21/03 were submitted late to the Agency. These reports include, but are not limited to:

Mfr. Cont.#	Product	Date Rec.	Date Sub.	Days Late	Reaction
M1008-2002	Pregnyl	8/26/02	10/1/02	174	Ectopic Pregnancy
M1321-2002	Remeron	8/16/02	12/23/02	114	Bilirubinemia
M0193-2003	Orgaran	8/20/02	3/5/03	182	Cerebral Infarction
M1362-2002	Orgaran	9/19/02	1/20/03	108	Pulmonary Embolism

2. **Failure to maintain records of all adverse drug experiences, including raw data relating to the adverse drug experiences. [21 CFR 314.80 (i)]**

Specifically, the adverse drug experience information received by phone is hand written on a scrap paper and then is discarded after being typed into an electronic format.

In your July 18 response, you state that some of the reporting delays were due to delays from affiliates getting the required information to NV Organon, Oss, the Netherlands, in a timely manner. Our review of several Council for International Organizations of Medical Sciences (CIOMS) reports seem to indicate that the adverse drug data was at NV Organon in ample time to be forwarded to Organon USA, for submission to the FDA within regulatory timeframes. For example, on CIOMS form, mfr. Control No. 2002-100842-NL, the date the adverse event was received at NV Organon was March 26, 2002, but the date it was sent to Organon, West Orange, NJ was September 30, 2002. Additional examples of late reporting to the West Orange, NJ facility from NV Organon can be seen in CIOMS reports, manufacturer control numbers, 2002-102264-NL and 2002-101153-NL.

Before any additional discussions on your most recent inspection, I would like to take this opportunity to briefly review your firm's past deficiencies regarding the timely submission of adverse drug experience reports to the FDA. In April of 1999, at the conclusion of an inspection of your West Orange, NJ facility, a FDA-483 was issued demonstrating that 65 out of 247 foreign 15-day ADE reports submitted from Organon in the Netherlands were submitted late to the Agency. Additionally, approximately 19 out of 194 domestic 15-day adverse drug reports were submitted late to the Agency. In response to these deficiencies [redacted] Senior Quality System

Specialist for Organon, West Orange, stated that all Organon personnel would be reminded about timely reporting and that the New Jersey facility would reiterate to Organon, the Netherlands, that 15 day ADE reports must be expedited to the West Orange, NJ facility.

On December 20, 2000, following an ADE inspection at Organon Teknika, Boxtel, the Netherlands, a warning letter was issued citing the late reporting of ADEs by this firm. In response to this warning letter, Mr. R. Salsmans, President, Organon Teknika, stated in a letter to Denis Mackey dated January 3, 2001, that the late reporting of ADEs by his facility would be addressed by hiring new personnel, revising SOPs, performing audits of affiliates and in holding international drug safety monitoring meetings. In an earlier correspondence dated September 26, 2000, [redacted] of Organon Teknika informed Gerald McGirl, FDA San Francisco Office, that some of the delays in the reporting of ADEs to the FDA from the Netherlands were due to the late reporting from international affiliates of Organon. They added that measures, such as training and auditing would be undertaken to assure that these affiliates would report ADEs to NV Organon in a more timely manner.

The continuing high incidence of late ADE reporting by Organon revealed during this most recent inspection seems to indicate that your past corrective actions may not have been effective. In response to the continuing late reporting of ADEs, you identified in your July 18 response the implementation of certain corrective actions, including re-training staff on ADE reporting procedures, monitoring international affiliates, visiting affiliated sites, revising SOPs, and holding periodic international safety meetings. Similar corrective actions implemented after the 1999 inspection have not been successful to date in significantly improving the timeliness of Organon's ADE reporting to FDA. We would appreciate information detailing how you plan to monitor the success of your corrective actions. This may include documentation that the number of late reports have been reduced over a specified time period. The FDA expects drug manufacturers to establish reasonable mechanisms to assure that all adverse drug experiences (ADE) are recorded, evaluated and submitted to the FDA within established timeframes as required under 21 CFR 314.80.

Neither the above list of deviations nor the Form FDA 483 Inspectional Observations, which was presented to and discussed with you at the conclusion of the inspection, are intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to ensure adherence to each requirement of the Act and its regulations.

Federal agencies are routinely advised of Warning Letters issued so that they may take this information into account when considering the award of government contracts.

Please be advised that pre-approval coverage was also conducted during this inspection, for [redacted] and [redacted]. New Jersey District has recommended to the Center for Drug Evaluation and Research (CDER) that these [redacted] be placed in withhold status. Notification of final agency action on these [redacted] will be issued from CDER.

You should take prompt action to correct deficiencies at your facility. Failure to implement corrective measures may result in further regulatory action without notice. These actions may include seizure of your products or injunction.

You should notify this office in writing within 15 working days of receipt of this letter of your additional corrective action plan to address the deficiencies at your firm. If corrective actions cannot be completed within 15 working days, please state the reason for the delay and the timeframe within which corrective actions will be completed. Your reply should be addressed to the New Jersey District Office, Food and Drug Administration, 10 Waterview Blvd., Parsippany, New Jersey 07054, Attn: Joseph F. McGinnis R.Ph, Compliance Officer.

Sincerely,

Douglas I. Ellsworth
District Director
New Jersey District